NARRATIVE REVIEW

Mesenchymal stem cells and its translation into clinical orthodontics: current trends and future perspectives

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Abstract

Oral mesenchymal stem cell populations in humans have been discovered in close vicinity to oral mucosal tissues and both primary (deciduous) and secondary (permanent) teeth. All these different kinds of stem cells have the ability to divide and replenish themselves, however they vary in their gene expression profiles and their capacity to give rise to distinct cell lineages. They all have multipotentiality i.e. chondrogenic, osteogenic, adipogenic, and neurogenic. Due to their relative accessibility, these cell types may form a source of stem cells with substantial potential for application in tissue regeneration. In this review, discoveries outlining stem cell potential are discussed on various aspects as, are their various applications in orthodontics i.e. orthodontic tooth movement, fixing external root resorption, correcting craniofacial anomalies, accelerating craniofacial distraction osteogenesis, recreating the TMJ, and ensuring a stable maxillary expansion.

Keywords: Cell, Osteogenesis, Transcriptome, Orthodontics, Stem Cells, Membrane, Temporomandibular

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Introduction

In multicellular organisms, stem cells are undifferentiated cells with the ability to self-renew or transform into a variety of cell types. In the early embryo, archetypal totipotent stem cells contain tissue-specific and extraembryonic stem cells. These totipotent stem cells have the potential to differentiate into every cell, however, multipotent mesenchymal stem cells (MSCs) are found in tissue of adult or mature tissue where they show limited potency to develop into different cell types. These cells are frequently called adult stem cells and include a haematopoietic system that can differentiate into a variety of blood components, including red blood cells and platelets. MSCs are found in several organs and tissues, and their function is to replace specific cell types during normal tissue repair or homeostasis.

There are a variety of ways to define stem cells. The definition of stem cells is evolving in the face of growing body of data about stem cells. Stem cells retain a high degree of flexibility even in adults. The following concepts are fundamental to the definition of stem cells: (1) self-rejuvenation (2) Multigenerational divergence from a common ancestor cell and (3) Regeneration of a tissue's functional capabilities in vivo.[1,2] What makes MSCs appealing for use in clinical practice is that they can be taken out of a living organism, kept separate, grown in large numbers, and then transplanted into another living organism where they will function as intended. (Table I) These cells may be organ-specific or non-organic-specific. Totipotent and pluripotent nature of stem cells that can be differentiated into many lineages make them more desirable, but, the immunological and ethical consequences of employing these cells make them less attractive. MSCs from the oral cavity have lately garnered interest as a potentially novel cell source owing to their potential therapeutic applications and simplicity of harvesting.

Oral MSCS

The several MSC populations seen in oral tissues have been given names that often reflect their place of anatomical origin. (Figure) Those MSCs found in the mouth and teeth are known as oral/dental mesenchymal stem cells (DMSCs),[3,4] and it was in the extracted third permanent molar that the first dental stem cells were identified, some 20 years ago.[5] Similarly, and probably not unexpectedly, DMSCs have been discovered in the pulp of human deciduous teeth that have already been shed (SHED cells).[6] Furthermore, DMSCs as apical dental papilla and dental follicular progenitor stem cells have been identified from incomplete third molar root apical foramens.[7,8] The periodontal ligament, the sub-epithelial gingiva and mucosa, the gingival tissue itself, the oral mucosa lamina propria progenitor stem cells, and the gingiva-derived mesenchymal stem cells are additional sources of non-dental stem cells in the mouth.[9 10, 11]

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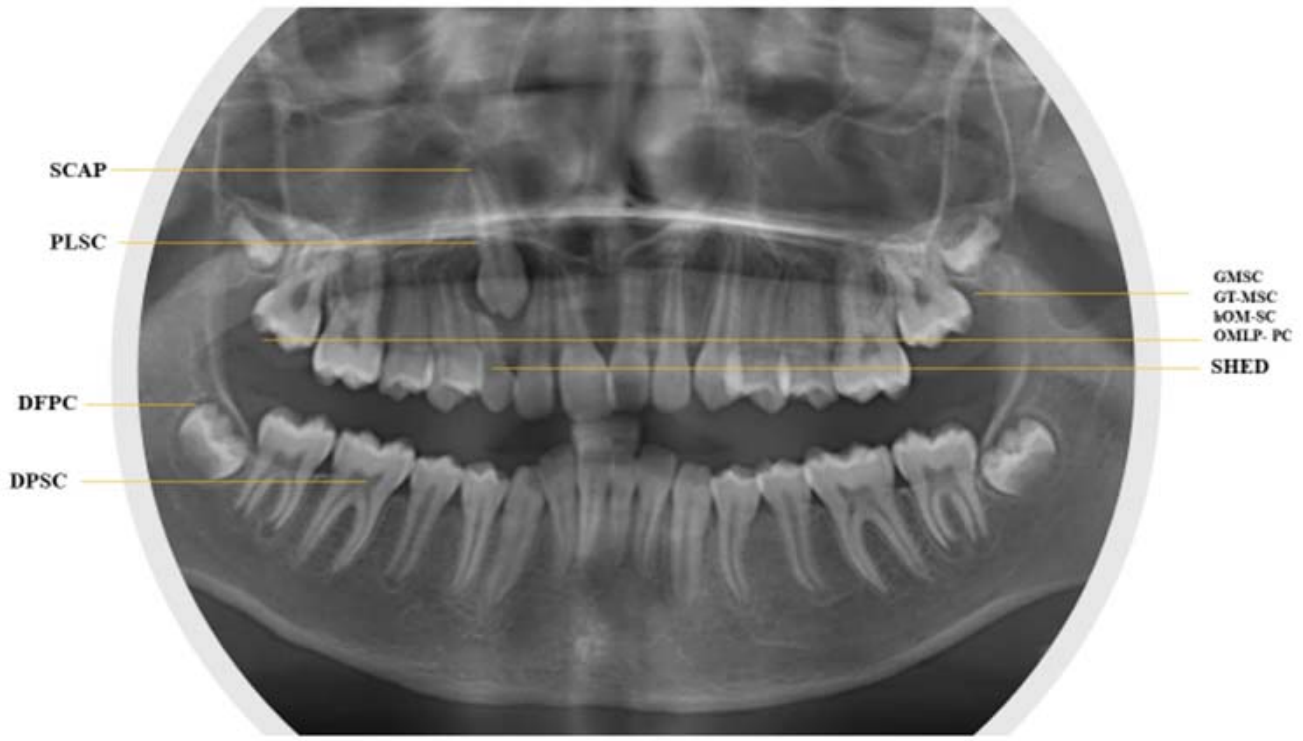

Figure: Sources of oral mesenchymal stem cells. Oral mesenchymal stem cells include dental pulp stem cells (DPSC) apical dental papilla (SCAP), dental follicle precursor stem cells (DFPC), Cells from human exfoliated deciduous teeth (SHED), Periodontal ligament stem cells (PLSC), Oral mucosa stem cells i.e gingiva derived mesenchymal stem cells (GMSC), gingival tissue-derived mesenchymal stem cells (GT-MSC), human oral mucosa stem cells (hOM-SC) and mucosa lamina properia progenitor cells (OMLP-PC).

Table-1: Differentiation of adult stem cells into craniofacial cell types and structures

Sources of Adult Stem Cells	Developing Unique Cell or Organ Types	Science Lab
Periodontal ligament	Cementum/Periodontal structures	Songtao Shi[72]
Bone marrow	Tooth structures and bone*	Paul T. Sharpe[73]
Pulp of the tooth	Dentine, odontoblast, pulp structures	Songtao Shi5
Tooth germ	Tooth structure	Pamela C. Yelick[74]
Bone marrow	Osteoblasts/osteocytes, Hematopoietic cells	Edwin M. Horwitzf[75]

All of these different kinds of stem cells have the ability to divide and replenish themselves, however they vary in their gene expression profiles and their capacity to give rise to distinct cell lineages.[12,13] They all have multipotentiality i.e. chondrogenic, osteogenic, adipogenic, and neurogenic. Stem cells from places like the apical foramen and the dental follicle can give rise to odontoblast like cells and a dentine-pulp-like complex, consistent with their anatomic location and the tissues from which they are harvested.[14,15]

Orthodontic applications of MSCS

Orthodontic tooth movement: Orthodontic tooth movement is caused by orthodontic forces to the teeth/periodontal ligament (PDL) and surrounding osseous structures, which results in remodelling processes.[16,17] Application of orthodontic force creates a compression site when the periodontal ligament (PDL) is compressed. This triggers an inflammatory cascade, which in turn recruits osteoclasts from the surrounding marrow spaces.[18] Haematopoietic stem cells are the primary source from which these osteoclasts are developed.[19] Hence, orthodontic tooth movement could be accelerated with the intervention of stem cells via supplying progenitor cells.

Little is known regarding the function and response of periodontal ligament stem cells during orthodontic force application. A study used a marker of stem cells i.e. CD90 on the rodent model to demonstrate the expression of stem cells in PDL. They discovered that the population of stem cells had increased at the compression site, but collagen-1 expression had reduced. However, when orthodontic forces were withdrawn, the expression of collagen-1 was restored. Hence, it can be hypothesized that it enhances orthodontic tooth movement via increasing the progenitor cells of osteoclasts and most

importantly, stabilizes the achieved tooth movement by production and maturation of collagen via expression of collagen-1.[20] An intriguing, if somewhat distant, prospect is the manipulation of PDL stem cell biology to speed up orthodontic tooth movement and, more crucially, to promote stability of tooth position.

External root resorption: One of the side effects of orthodontic tooth movement is external apical root resorption, which results in loss of cementum and dentine that may compromise the longevity of the tooth. The orthodontic treatment is halted when the severe root resorption is found and there is no treatment modality available to manage the resorbed root. However, now there is a hope where stem cells could be used as a potential solution to regenerate the cementum and there is reason to be hopeful that a viable source can be found, where the wide distribution and various anatomical locations of DMSCs are already discovered. Despite the fact that the aforementioned idea is still in its infancy, it has recently been discovered that when PDL stem cells were isolated by outgrowth, they were able to produce cellular cementum-like hard tissue including embedded osteocalcin-embedded cells forming in vivo transplantation.[21]

Rapid maxillary expansion: Maxillary constriction causes numerous occlusal and functional complications. It may induce a constricted oropharyngeal airway, a decrease in nasal airflow, and a change in position of the tongue, which may lead to a narrowing of the retroglossal airway and mouth breathing.[22-24] The treatment modalities to correct constricted maxilla consist of slow expansion of the maxilla, rapid expansion of the maxilla (RME), and surgical assisted expansion of maxilla.[25, 26] In children younger than 12 years age or patients with incompletely fused mid-palatal suture, RME is often advised. By opening the midpalatal suture via RME, an orthodontist can effectively enhance maxillary width, restore jaw-to-face proportions, and alleviate jaw-to-face pain.[27, 28] In RME, the two bone segments are separated by force, and the resulting space is filled with granulation tissue and blood before active bone formation begins. Without an adequate retention period, the maxillary arch widening achieved during orthodontics (RME) will revert to its original size. Accordingly, enhancing the rate at which bone forms in the void left by RME can reduce treatment and retention times and stabilize the treatment. Injecting the stem cells, which have the potential to develop into osteogenic cells, appears to hasten bone formation. Ekizer et al.[29] conducted an experiment on animals showing that injecting stem cells into a fractured intermaxillary suture led to an increase in the number of new blood vessels and osteoblasts, which in turn led to more bone growth. Thus patients undergoing RME may benefit from a shorter treatment and retention time if local DMSCs are applied to the expanded maxilla to stimulate new bone formation in the midpalatal suture.[30]

Envelope of discrepancy: The range of orthodontic tooth movement is limited by factors such as alveolar bone structure, soft tissue pressures, levels of periodontal attachment, neuromuscular forces, and tooth-lip relationships.[31,32] The envelope of discrepancy refers to the millimetric range of tooth movement in the sagittal, transverse, and vertical planes that can be achieved without compromising stability and ensuing side effects i.e. if maxillary teeth are expanded beyond the envelope, bone dehiscence and gingival recession are possible outcomes.[33] Defects like fenestration and dehiscence are inevitable at sites with thin buccal and lingual cortical plates and gingival biotype, especially in the case of lower incisors compensated with lingual inclinations and with prominent chin.[34, 35]

Stem cell treatment is a potential technique for the regeneration of alveolar bone because stem cells may produce many tissues, including bone. Human bone ridge augmentation by stem cell therapy has been attempted by some studies, with bone marrow cells being the primary source.[36-38] The results of regenerating alveolar bone had an inclination to improve bone growth.[39] As a result, bone regeneration techniques involving stem cells may offer a means of enlarging the potential range of error.

Hypothetically, osteogenesis based on stem cells might be used to augment the ridge horizontally, enhancing the stability of tooth movement/envelope of discrepancy and allowing the patient to surpass some restrictions, based on the findings of investigations on alveolar bone augmentation.

Dentofacial anomalies: Difficult-to-correct defects are a frequent clinical challenge in craniofacial surgery, such as those caused by congenital and developmental deformity, trauma, tumour removal, and non-union of fractures. In order to repair bone and soft tissue, modern surgical procedures have been used in conjunction with autogenous, allogeneic, and prosthetic materials.[40] Stem cell-based tissue regeneration presents a promising way to deliver an advanced and reliable therapeutic technique for craniofacial tissue repair, which could help patients overcome the difficulties of donor site morbidity, irregularities of contour, cost and lengthy surgery times.[41] Cleft lip and palate (CLP) and hemifacial microsomia are

discussed in this article as two examples of dentofacial anomalies.

Failure of the nasal process and oro-palatal shelves to fuse during development causes CLP, a common congenital anomaly. This anomaly affects 0.36 to 0.83 of every 1,000 newborns.[42] Repairing malformed alveolar bone corrects oronasal fistula, maxillary arch unification, tooth eruption, and alar base support. Autogenous cancellous bone grafts are the standard of care for reconstructing alveolar bone defects.[43] Grafts to the alveolar cleft have an 88% success rate with respect to bone resorption, and the most common site for extracting autogenous bone for transplantation is the anterior iliac crest.[44] The development of tissue engineering has resulted in the availability of several bone grafts apart from the conventional iliac crest graft. There is evidence that MSCs can generate new bone after being implanted in the cleft region.[45-50] (Table: II)

Table-2: Research showing results of MSCs usage to regenerate alveolar cleft.

Author/Year/Study Design/Sample Size	Carrier	Cell type	Growth factor	Result
Behnia et al.[46] / /2009/CR/02	Osteoset (calcium sulphate) + demineralised bone mineral	Mesenchymal stem cells from bone marrow aspirate of posterior Iliac crest	-	34.5% bone formation
Hibi et al. [47] / Italy/2006/CR/01	-	Mesenchymal stem cells (marrow aspirate)	-	79.1.5% bone formation
Stanko et al.[48] / /2013/CR/01	Collagen membrane/Hydroxyapatite particles	Mesenchymal stem cells (pelvic bone marrow aspirate)	Platelet rich plasma.	Initial bone formation in oronasal fistula after 10 weeks
Behnia et al.[49] / /2012/Preliminary/03	Biphasic scaffold	Mesenchymal stem cells from bone marrow aspirate of posterior Iliac crest	Platelet derived growth factor	51.3% bone formation
Carstanjen et al.[50] / /2012/Animal/01	Injection	Autologous Mesenchymal stem cells		90% defect correction of sof palate defect after 14 days

Hemifacial microsomia is the second most common congenital syndrome, following cleft lip and palate, that results after aberration in first and second pharyngeal arches that leads to unilateral abnormality on the face.[51] Congenital and posttraumatic soft tissue abnormalities can be repaired with grafting of autologous fat.[52] Fat grafting results are uncertain and have a low survival rate, despite various novel initiatives and advancements of surgical techniques.[53] Adipose derived stromal cells (ASCs) have recently gained popularity because of their potential to be used in tissue regeneration. At six months, individuals with hemifacial microsomia whose grafts were augmented with ASCs had 88% fat volume survival, compared to 54% in the control group.[54] In addition, ASC-enriched grafts had greater amounts of residual tissue following transplantation compared to the control group.[55]

The long-term effects of these kinds of therapies need to be investigated as additional data from studies become available. Angiogenesis, transplant survival, and atrophy can all be improved by using ASCs to repair soft tissue, according to the literature.[54-56]

Disorders of temporomandibular joint: The temporomandibular joint (TMJ) is the cartilaginous and osseous structure that connects the mandible to the skull. It has two articular surfaces that can adjust to different environments and is protected by a capsule that is constantly being lubricated by synovial fluid, making it a crucial growth site for post-natal growth.[57,58] Condyle-region progenitor/stem cells differentiate into chondrocytes that produce condylar matrix, which then differentiates into lamellar bone hence making up the condyle.[59] Since stem cells can differentiate into both chondrogenic and osteogenic lineages, they may be effective for maintaining the altered position of the jaw and treating TMJ injuries.

Patients with mandibular deficit typically receive a functional appliance that positions the mandible forward. This position causes an increase in stem cells in the TMJ fossa, culminating in the production of new bones. In this context, the question will be that can injection of stem cells into the temporal fossa during functional appliance therapy or any destructive TMJ condition increase new bone formation in the temporal fossa? This needs to be explored in further studies.

The TMJ is vulnerable to trauma, malignancy,

osteoarthritis, rheumatoid arthritis, and congenital abnormalities. Surgery to replace the mandibular condyle is often the first and only option for individuals with severe degenerative diseases.[60] However, these approaches can lead to infection, immune-rejection, implant wear, insufficient biocompatibility, dislocation, donor site limits and morbidity, and even pathogen transfer.[61,62] Engineering of osteochondral tissue have devised strategies to overcome them by developing medically and mechanically effective tissue. Rebuilding joints with these cells has recently gained a great deal of attention.

Numerous studies have looked into the feasibility of engineering an osteochondral transplant with a TMJ-like structure. The cultivation of human umbilical cord stem cells with chondrogenic stimuli revealed that human umbilical cord matrix stem cells can surpass TMJ cartilage cells.[63] Mesenchymal stem cells isolated from rat bone marrow, cultured in a hydrogel composed of ethylene glycol, and moulded into the form of a human cadaver condyle showed a combination of cartilaginous and osseous morphologies.[64,65]

Though studies have revealed that TMJ bone and cartilage can regenerate, the TMJ disc is made of fibrocartilage, and there has been minimal success in making synthetic TMJ discs; thus, the focus has switched to engineering to repair the disc.[66] Tissue-engineered TMJ discs were developed in one study by fusing polylactide acid discs and stem cells from adipose tissue.[67] Human clinical trials have not yet been completed, however studies are now underway using animal models to reproduce the osteochondral interface and develop TMJ. In the light of these results, combining SCs with various scaffolds may be an effective method for repairing the osteochondral tissues of the TMJ and, ultimately, the joint disc.

Distraction osteogenesis: Endogenous bone tissue engineering, or "DO," is commonly utilized in orthopaedic surgery for the correction of various craniofacial deformities and the restoration of limb length.[68] By accelerating osteogenesis in the distraction Gap and decreasing the consolidation phase, nonunion, infection, and fracture can be reduced. Recent studies have shown that stem cells can stimulate bone formation and shorten the consolidation phase during DO, perhaps because of the engagement of MSCs in osteogenesis. Human exfoliated deciduous teeth (SHED), bone marrow, and adipose tissue are just a few of the places where SCs have been used in research to promote DO.[69-71]

Conclusion and Future Perspectives

Oral mesenchymal stem cells are a valuable and easily accessible stem cell source with potential use in orthodontics and other regenerative dental therapy. However, the use of these stem cells in clinical orthodontics is still a matter of debate due to lack of high quality of evidence. Research in many fields, such as cell biology and tissue regeneration, will be required to improve our ability to regulate their behaviour in vivo. However, it is also vital to understand how these cells may be recognized, collected, expanded, and, most significantly, maintain their in vitro characteristics. Almost certainly, the rate of development is at a rapid pace.

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References

1. Clevers H, Watt FM. Defining Adult Stem Cells by Function, not by Phenotype. Annu Rev Biochem 2018;87:1015-27. doi: 10.1146/annurev-biochem-062917-012341.
2. Sanz JL, Guerrero-Gironés J, Pecci-Lloret MP, Pecci-Lloret MR, Melo M. Biological interactions between calcium silicate-based endodontic biomaterials and periodontal ligament stem cells: A systematic review of in vitro studies. Int Endod J 2021;54:2025-43. doi: 10.1111/iej.13600.
3. Sharpe PT. Dental mesenchymal stem cells. Development 2016;143:2273-80. doi: 10.1242/dev.134189.
4. Xiao L, Nasu M. From regenerative dentistry to regenerative medicine: progress, challenges, and potential applications of oral stem cells. Stem Cells Cloning 2014;7:e89-99. doi: 10.2147/SCCAA.S51009.
5. Gronthos S, Mankani M, Brahim J, Robey PG, Shi S. Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. Proc Natl Acad Sci 2000;97:13625-30. doi: 10.1073/pnas.240309797.
6. Miura M, Gronthos S, Zhao M, Lu B, Fisher LW, Robey PG, et al. SHED: stem cells from human exfoliated deciduous teeth. Proc Natl Acad Sci 2003;100:5807-12. doi: 10.1073/pnas.0937635100.
7. Gan L, Liu Y, Cui D, Pan Y, Zheng L, Wan M. Dental Tissue-Derived Human Mesenchymal Stem Cells and Their Potential in Therapeutic Application. Stem Cells Int 2020;2020:e8864572. doi: 10.1155/2020/8864572.
8. Sequeira DB, Oliveira AR, Seabra CM, Palma PJ, Ramos C, Figueiredo MH, et al. Regeneration of pulp-dentin complex using human stem cells of the apical papilla: in vivo interaction with two bioactive materials. Clin Oral Investig 2021;25:5317-29. doi: 10.1007/s00784-021-03840-9.
9. Trubiani O, Pizzicannella J, Caputi S, Marchisio M, Mazzon E, Paganelli R, et al. Periodontal Ligament Stem Cells: Current Knowledge and Future Perspectives. Stem Cells Dev 2019;28:995-1003. doi: 10.1089/scd.2019.0025.
10. Yuan X, Xu Q, Zhang X, Van Brunt LA, Ticha P, Helms JA. Wnt-Responsive Stem Cell Fates in the Oral Mucosa. iScience 2019;21:84-94. doi: 10.1016/j.isci.2019.10.016.
11. Kim D, Lee AE, Xu Q, Zhang Q, Le AD. Gingiva-Derived Mesenchymal Stem Cells: Potential Application in Tissue Engineering and Regenerative Medicine - A Comprehensive Review. Front Immunol 2021;12:e667221. doi: 10.3389/fimmu.2021.667221.
12. Trubiani O, Marconi GD, Pierdomenico SD, Piattelli A, Diomede F,

Pizzicannella J. Human Oral Stem Cells, Biomaterials and Extracellular Vesicles: A Promising Tool in Bone Tissue Repair. Int J Mol Sci 2019;20:4987. doi: 10.3390/ijms20204987.
13. Spagnuolo G, Codispoti B, Marrelli M, Rengo C, Rengo S, Tatullo M. Commitment of Oral-Derived Stem Cells in Dental and Maxillofacial Applications. Dent J (Basel) 2018;6:72. doi: 10.3390/dj6040072.
14. Shi X, Mao J, Liu Y. Pulp stem cells derived from human permanent and deciduous teeth: Biological characteristics and therapeutic applications. Stem Cells Transl Med 2020;9:445-64. doi: 10.1002/sctm.19-0398.
15. Han J, Kim DS, Jang H, Kim HR, Kang HW. Bioprinting of three-dimensional dentin-pulp complex with local differentiation of human dental pulp stem cells. J Tissue Eng 2019;10:e2041731419845849. doi: 10.1177/2041731419845849.
16. Li Y, Zhan Q, Bao M, Yi J, Li Y. Biomechanical and biological responses of periodontium in orthodontic tooth movement: up-date in a new decade. Int J Oral Sci 2021;13:20. doi: 10.1038/s41368-021-00125-5.
17. Theodorou CI, Kuijpers-Jagtman AM, Bronkhorst EM, Wagener FADTG. Optimal force magnitude for bodily orthodontic tooth movement with fixed appliances: A systematic review. Am J Orthod Dentofacial Orthop 2019;156:582-92. doi: 10.1016/j.ajodo.2019.05.011.
18. Li Y, Jacox LA, Little SH, Ko CC. Orthodontic tooth movement: The biology and clinical implications. Kaohsiung J Med Sci 2018;34:207-14. doi: 10.1016/j.kjms.2018.01.007.
19. Ogawa S, Kitaura H, Kishikawa A, Qi J, Shen WR, Ohori F, et al. TNF-α is responsible for the contribution of stromal cells to osteoclast and odontoclast formation during orthodontic tooth movement. PLoS One 2019;14:e0223989. doi: 10.1371/journal.pone.0223989.
20. Feng L, Yang R, Liu D, Wang X, Song Y, Cao H, et al. PDL Progenitor-Mediated PDL Recovery Contributes to Orthodontic Relapse. J Dent Res 2016;95:1049-56. doi: 10.1177/0022034516648604.
21. Liu J, Ruan J, Weir MD, Ren K, Schneider A, Wang P, et al. Periodontal Bone-Ligament-Cementum Regeneration via Scaffolds and Stem Cells. Cells 2019;8:537. doi: 10.3390/cells8060537.
22. Bucci R, Montanaro D, Rongo R, Valletta R, Michelotti A, D'Antò V. Effects of maxillary expansion on the upper airways: Evidence from systematic reviews and meta-analyses. J Oral Rehabil 2019;46:377-87. doi: 10.1111/joor.12766.
23. Cerritelli L, Hatzopoulos S, Catalano A, Bianchini C, Cammaroto G, Meccariello G, et al. Rapid Maxillary Expansion (RME): An Otolaryngologic Perspective. J Clin Med 2022;11:5243. doi: 10.3390/jcm11175243.
24. Furche S, Edwards SP, Aronovich S, Hummon G, Shah KB, Conley RS. 3D Airway changes using cone beam computed tomography in patients following mandibular advancement surgery with and without constriction. Orthod Craniofac Res 2019;22(Suppl 1):s36-42. doi: 10.1111/ocr.12292.
25. Carvalho PHA, Moura LB, Trento GS, Holzinger D, Gabrielli MAC, Gabrielli MFR, et al. Surgically assisted rapid maxillary expansion: a systematic review of complications. Int J Oral Maxillofac Surg 2020;49:325-32. doi: 10.1016/j.ijom.2019.08.011.
26. Lanteri V, Farronato M, Ugolini A, Cossellu G, Gaffuri F, Parisi FMR, et al. Volumetric Changes in the Upper Airways after Rapid and Slow Maxillary Expansion in Growing Patients: A Case-Control Study. Materials (Basel) 2020;13:2239. doi: 10.3390/ma13102239.
27. Kapetanović A, Theodorou CI, Bergé SJ, Schols JGJH, Xi T. Efficacy of Miniscrew-Assisted Rapid Palatal Expansion (MARPE) in late adolescents and adults: a systematic review and meta-analysis. Eur J Orthod 2021;43:313-23. doi: 10.1093/ejo/cjab005.
28. Jesus AS, Oliveira CB, Murata WH, Gonçales ES, Pereira-Filho VA, Santos-Pinto A. Nasomaxillary effects of miniscrew-assisted rapid palatal expansion and two surgically assisted rapid palatal expansion approaches. Int J Oral Maxillofac Surg 2021;50:1059-68. doi: 10.1016/j.ijom.2020.12.014.
29. Ekizer A, Yalvac ME, Uysal T, Sonmez MF, Sahin F. Bone marrow mesenchymal stem cells enhance bone formation in orthodontically expanded maxillae in rats. Angle Orthod 2015;85:394-9. doi: 10.2319/031114-177.1.
30. Ebadifar A, Eslamian L, Motamedian SR, Badiee MR, Mohaghegh S, Farahani M, et al. Effect of mesenchymal stem cells with platelet-rich plasma carriers on bone formation after rapid maxillary expansion: An Animal Study. Orthod Craniofac Res 2022;25:151-8. doi: 10.1111/ocr.12518.
31. Hasan HS, Elkolaly MA. Updating the orthodontic envelope of discrepancy: Canines transposition. Int J Orthod Rehabil 2021;12:140-7. DOI: 10.4103/ijor.ijor_24_21
32. Fleming PS. Orthodontic treatment planning: can we plan for stability? Br Dent J 2021;230:717-21. doi: 10.1038/s41415-021-2891-5.
33. Morais JF, Melsen B, de Freitas KMS, Castello Branco N, Garib DG, Cattaneo PM. Evaluation of maxillary buccal alveolar bone before and after orthodontic alignment without extractions: A cone beam computed tomographic study. Angle Orthod 2018;88:748-56. doi: 10.2319/101117-686.1.
34. Proffit WR, Fields HW Jr, Sarver DM. Contemporary Orthodontics, 4th ed. St. Louis, Missouri: Mosby/Elsevier, 2007; pp 207-17.
35. Preoteasa CT, Ionescu E, Preoteasa E. Risks and complications associated with orthodontic treatment. Orthod Asp Clin Consid 2012;2012:403-28.
36. Rickert D, Sauerbier S, Nagursky H, Menne D, Vissink A, Raghoebar GM. Maxillary sinus floor elevation with bovine bone mineral combined with either autogenous bone or autogenous stem cells: a prospective randomized clinical trial. Clin Oral Implants Res 2011;22:251-8. doi: 10.1111/j.1600-0501.2010.01981.x.
37. Payer M, Lohberger B, Strunk D, Reich KM, Acham S, Jakse N. Effects of directly autotransplanted tibial bone marrow aspirates on bone regeneration and osseointegration of dental implants. Clin Oral Implants Res 2014;25:468-74. doi: 10.1111/clr.12172.
38. Yamada Y, Nakamura S, Ueda M, Ito K. Osteotome technique with injectable tissue-engineered bone and simultaneous implant placement by cell therapy. Clin Oral Implants Res 2013;24:468-74. doi: 10.1111/j.1600-0501.2011.02353.x.
39. Miguita L, Mantesso A, Pannuti CM, Deboni MCZ. Can stem cells enhance bone formation in the human edentulous alveolar ridge? A systematic review and meta-analysis. Cell Tissue Bank 2017;18:217-28. doi: 10.1007/s10561-017-9612-y.
40. Moussa NT, Dym H. Maxillofacial Bone Grafting Materials. Dent Clin North Am 2020;64:473-90. doi: 10.1016/j.cden.2019.12.011.
41. Miura M, Miura Y, Sonoyama W, Yamaza T, Gronthos S, Shi S. Bone marrow-derived mesenchymal stem cells for regenerative medicine in craniofacial region. Oral Dis 2006;12:514-22. doi: 10.1111/j.1601-0825.2006.01300.x.
42. Luaces-Rey R, Arenaz-Búa J, Lopez-Cedrún-Cembranos JL, Herrero-Patiño S, Sironvalle-Soliva S, Iglesias-Candal E, et al. Is PRP useful in alveolar cleft reconstruction? Platelet-rich plasma in secondary alveoloplasty. Med Oral Patol Oral Cir Bucal 2010;15:e619-23. doi: 10.4317/medoral.15.e619.
43. Nwoku AL, Al Atel A, Al Shlash S, Oluyadi BA, Ismail S. Retrospective analysis of secondary alveolar cleft grafts using iliac of chin bone. J Craniofac Surg 2005;16:864-8. doi: 10.1097/01.scs.0000179742.45424.0a.
44. Eufinger H, Leppänen H. Iliac crest donor site morbidity following open and closed methods of bone harvest for alveolar cleft osteoplasty. J Craniomaxillofac Surg 2000;28:31-8. doi: 10.1054/jcms.2000.0105.

45. Horswell BB, Henderson JM. Secondary osteoplasty of the alveolar cleft defect. J Oral Maxillofac Surg 2003;61:1082-90. doi: 10.1016/s0278-2391(03)00322-7.
46. Behnia H, Khojasteh A, Soleimani M, Tehranchi A, Khoshzaban A, Keshel SH, et al. Secondary repair of alveolar clefts using human mesenchymal stem cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;108:e1-6. doi: 10.1016/j.tripleo.2009.03.040.
47. Hibi H, Yamada Y, Ueda M, Endo Y. Alveolar cleft osteoplasty using tissue-engineered osteogenic material. Int J Oral Maxillofac Surg 2006;35:551-5. doi: 10.1016/j.ijom.2005.12.007.
48. Stanko P, Mracna J, Stebel A, Usakova V, Smrekova M, Vojtassak J. Mesenchymal stem cells - a promising perspective in the orofacial cleft surgery. Bratisl Lek Listy 2013;114:50-2. doi: 10.4149/bll_2013_012.
49. Behnia H, Khojasteh A, Soleimani M, Tehranchi A, Atashi A. Repair of alveolar cleft defect with mesenchymal stem cells and platelet derived growth factors: a preliminary report. J Craniomaxillofac Surg 2012;40:2-7. doi: 10.1016/j.jcms.2011.02.003.
50. Carstanjen B, Desbois C, Hekmati M, Behr L. Successful engraftment of cultured autologous mesenchymal stem cells in a surgically repaired soft palate defect in an adult horse. Can J Vet Res 2006;70:143-7.
51. Lei Y, Mao L, Zhu H, Yao J. Development of catechol-functionalized chitosan/poly (vinyl alcohol) nanocomposite films incorporated with dual network coated layered clay for active packaging applications. J Appl Polym Sci. 2021;138:51-55.
52. Clauser LC, Tieghi R, Galiè M. Fat Grafting in Soft Tissue Augmentation. In: Perry M, Holmes S, eds. Atlas of Operative Maxillofacial Trauma Surgery: Post-Traumatic Deformity, 1st ed. London, UK: Springer-Verlag London Ltd, 2020; pp 237-50. doi: 10.1007/978-1-4471-5616-1_17
53. Doornaert M, Colle J, De Maere E, Declercq H, Blondeel P. Autologous fat grafting: Latest insights. Ann Med Surg (Lond) 2018;37:47-53. doi: 10.1016/j.amsu.2018.10.016.
54. Tanikawa DYS, Aguena M, Bueno DF, Passos-Bueno MR, Alonso N. Fat grafts supplemented with adipose-derived stromal cells in the rehabilitation of patients with craniofacial microsomia. Plast Reconstr Surg 2013;132:141-52. doi: 10.1097/PRS.0b013e3182910a82.
55. Kølle SF, Fischer-Nielsen A, Mathiasen AB, Elberg JJ, Oliveri RS, Glovinski PV, et al. Enrichment of autologous fat grafts with ex-vivo expanded adipose tissue-derived stem cells for graft survival: a randomised placebo-controlled trial. Lancet 2013;382:1113-20. doi: 10.1016/S0140-6736(13)61410-5.
56. Tabit CJ, Slack GC, Fan K, Wan DC, Bradley JP. Fat grafting versus adipose-derived stem cell therapy: distinguishing indications, techniques, and outcomes. Aesthetic Plast Surg 2012;36:704-13. doi: 10.1007/s00266-011-9835-4.
57. Joshi AS, Hatch NE, Hayami T, Jheon A, Kapila S. IGF-1 TMJ injections enhance mandibular growth and bone quality in juvenile rats. Orthod Craniofac Res 2022;25:183-91. doi: 10.1111/ocr.12524.
58. Lin Y, Umebayashi M, Abdallah MN, Dong G, Roskies MG, Zhao YF, et al. Combination of polyetherketoneketone scaffold and human mesenchymal stem cells from temporomandibular joint synovial fluid enhances bone regeneration. Sci Rep 2019;9:472. doi: 10.1038/s41598-018-36778-2.
59. St-Jacques B, Hammerschmidt M, McMahon AP. Indian hedgehog signaling regulates proliferation and differentiation of chondrocytes and is essential for bone formation. Genes Dev 1999;13:2072-86. doi: 10.1101/gad.13.16.2072.
60. Elledge R, Mercuri LG, Attard A, Green J, Speculand B. Review of emerging temporomandibular joint total joint replacement systems. Br J Oral Maxillofac Surg 2019;57:722-8. doi: 10.1016/j.bjoms.2019.08.009.
61. Chigurupati R, Mehra P. Surgical Management of Idiopathic Condylar Resorption: Orthognathic Surgery Versus Temporomandibular Total Joint Replacement. Oral Maxillofac Surg Clin North Am 2018;30:355-67. doi: 10.1016/j.coms.2018.05.004.
62. Upadya VH, Bhat HK, Rao BHS, Reddy SG. Classification and surgical management of temporomandibular joint ankylosis: a review. J Korean Assoc Oral Maxillofac Surg 2021;47:239-48. doi: 10.5125/jkaoms.2021.47.4.239.
63. Minervini G, Del Mondo D, Russo D, Cervino G, D'Amico C, Fiorillo L. Stem Cells in Temporomandibular Joint Engineering: State of Art and Future Persectives. J Craniofac Surg 2022;33:2181-7. doi: 10.1097/SCS.0000000000008771.
64. Alhadlaq A, Mao JJ. Tissue-engineered neogenesis of human-shaped mandibular condyle from rat mesenchymal stem cells. J Dent Res 2003;82:951-6. doi: 10.1177/154405910308201203.
65. Alhadlaq A, Elisseeff JH, Hong L, Williams CG, Caplan AI, Sharma B, et al. Adult stem cell driven genesis of human-shaped articular condyle. Ann Biomed Eng 2004;32:911-23. doi: 10.1023/b:abme.0000032454.53116.ee.
66. Lin Y, Lin H, Ramamoorthi M, Wu DT, Zhang Z, Tran SD. Scaffolds for temporomandibular joint disc engineering. In: Mozafari M, Sefat F, Atala A, eds. Handbook of Tissue Engineering Scaffolds: Volume One, 1st ed. Duxford, UK: Woodhead Publishing, Elsevier Ltd, 2019; pp 437-55.
67. Karic V, Chandran R, Abrahamse H. 940 nm diode laser induced differentiation of human adipose derived stem cells to temporomandibular joint disc cells. BMC Biotechnol 2022;22:23. doi: 10.1186/s12896-022-00754-6.
68. Chappell TM, Ebert CC, McCann KM, Hutchinson BL, Rodriguez-Collazo E. Distal tibial distraction osteogenesis-an alternative approach to addressing limb length discrepancy with concurrent hindfoot and ankle reconstruction. J Orthop Surg Res 2019;14:244. doi: 10.1186/s13018-019-1264-0.
69. Ma D, Ren L, Yao H, Tian W, Chen F, Zhang J, et al. Locally injection of cell sheet fragments enhances new bone formation in mandibular distraction osteogenesis: a rabbit model. J Orthop Res 2013;31:1082-8. doi: 10.1002/jor.22336.
70. Hu J, Qi MC, Zou SJ, Li JH, Luo E. Callus formation enhanced by BMP-7 ex vivo gene therapy during distraction osteogenesis in rats. J Orthop Res 2007;25:241-51. doi: 10.1002/jor.20288.
71. Sun JJ, Zheng XH, Wang LY, Liu L, Jing W, Lin YF, et al. New bone formation enhanced by ADSCs overexpressing hRunx2 during mandibular distraction osteogenesis in osteoporotic rabbits. J Orthop Res 2014;32:709-20. doi: 10.1002/jor.22590.
72. Seo BM, Miura M, Gronthos S, Bartold PM, Batouli S, Brahim J, et al. Investigation of multipotent postnatal stem cells from human periodontal ligament. Lancet 2004;364:149-55. doi: 10.1016/S0140-6736(04)16627-0.
73. Ohazama A, Modino SA, Miletich I, Sharpe PT. Stem-cell-based tissue engineering of murine teeth. J Dent Res 2004;83:518-22. doi: 10.1177/154405910408300702.
74. Duailibi MT, Duailibi SE, Young CS, Bartlett JD, Vacanti JP, Yelick PC. Bioengineered teeth from cultured rat tooth bud cells. J Dent Res 2004;83:523-8. doi: 10.1177/154405910408300703.
75. Dominici M, Pritchard C, Garlits JE, Hofmann TJ, Persons DA, Horwitz EM. Hematopoietic cells and osteoblasts are derived from a common marrow progenitor after bone marrow transplantation. Proc Natl Acad Sci U S A 2004;101:11761-6. doi: 10.1073/pnas.0404626101.